REMARKS

Reconsideration is requested.

Claims 1-32 are pending. Claims 11-32 have been withdrawn from consideration. Claims 1-10 are believed to be under active consideration, as stated on page 1 of the Office Action dated February 14, 2008.

Page 2 of the Office Action dated February 14, 2008 confirms that claims 1-10 read on the elected subject matter of the Examiner's Group I. The Examiner however also indicates that only claims 1-9 are under consideration. Claim 10 is also presumed to be under active consideration, as reading on the elected subject matter. See also page 2 of the Office Action dated November 5, 2007. Clarification of the record is requested in this regard.

The claims have been amended, without prejudice, to advance prosecution. Support for the revision to claim 2 is believed to exist, for example, in the disclosure on page 11, lines 4-5. No new matter has been added.

While acknowledging that the present application is a U.S. national phase of a PCT application, the Examiner further appears to require a certified copy of the PCT application, in a manner similar to a foreign priority document. See page 2 of the Office Action dated February 14, 2008. The Examiner is urged to appreciate that the PCT application is a U.S. application according to, for example, 35 USC § 363. The applicants have not claimed benefit of a separate "application filed in Great Britain on July 3, 2003", as suggested by the Examiner on page 2 of the Office Action dated February 14, 2008 and a certified copy of the PCT application should not be required.

The Examiner is requested to provide a basis in the Law, Rules and/or MPEP in the event the requirement is maintained.

The Abstract has been revised to advance prosecution. No new matter has been added. The amendment is made without prejudice. Withdrawal of the objection to the Abstract is requested.

The specification has been revised above by adding a heading for the Brief Description of the Drawings on page 20, line 20. No new matter has been added. The Examiner's reference to the suggestions of Rule 77(b) is noted however the Examiner will appreciate that the layout for a patent specification outlined in Rule 77(b) is not a requirement of the Rules (i.e., "the specification should include the following"). The above amendment to the specification is submitted to be an "Appropriate action" in response to the Examiner's comments.

The cross-reference to the PCT application has been corrected above, as suggested by the Examiner. No new matter has been added.

The title has been amended according to the Examiner's helpful suggestion.

The objection to claim 4 is not understood and clarification is requested in the event anything further is required. Specifically, the following is a reproduction of claim 4 from the PTO IFW:

> 4. (Original) A method according to claim 3 wherein the taxane is paclitaxel or a derivative thereof.

The second line of claim 4 is not believed to begin with the number "4", as stated by the Examiner on page 8 of the Office Action dated February 14, 2008. The pending

claims are presented above with the noted additional revisions. The Examiner is requested to advise the undersigned of any further basis for objecting to claim 4. Alternatively, withdrawal of the objection is requested.

The Section 112, second paragraph, rejection of claim 2 is obviated by the above amendments.

While claim 4 is stated to be rejected under Section 112, second paragraph, on page 9 of the Office Action dated February 14, 2008, there is no stated basis for the rejection. Clarification is requested in the event any rejection under Section 112, second paragraph, is maintained in a further Action.

To the extent not obviated by the above, the Section 112, first paragraph "written description", rejection of claim 4 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following.

The derivative of claim 4 is a taxane, as described, for example on page 2, lines 33-34 of the specification. One of ordinary skill will appreciate that taxanes are complex esters consisting of a 15-member taxane ring system linked to a four-member oxetan ring (page 2, lines 20-21). Thus, claim 4 specifies the structure of the claimed paclitaxel derivatives.

Structures of exemplary paclitaxel derivatives are also described, for example, on page 2, line 33, to page 3, line 33, of the application. Specifically, it is disclosed that many paclitaxel derivatives were already known in the art at the filing date of the present application (page 3, lines 2-5). Exemplary derivations, e.g. 'acylation at the C-7 hydroxyl group, or its replacement with hydrogen' or 'replacement of the 10-acetoxy

group with hydrogen', are also disclosed (page 3, lines 5-10). In addition, a number of exemplary paclitaxel derivatives are listed on page 3, lines 29-33.

The applicants submit that the specification describes an adequate written description of structures of paclitaxel derivatives. The applicants were in possession of claimed invention at the filing date of the present application, as well as a sufficient number of species of structure(s) of the recited derivatives to support possession of the genus.

The applicants further submit the attached two references, Miller et al. ("Chemistry and Chemical Biology of Taxane Anticancer Agents" The Chemical Record, Vol. 1, 195-211 (2001)) and Kingston et al. ("Taxoids: Cancer-fighting compounds from nature" Current Opinion in Drug Discovery & Development 2007 10(2): 130-144 (2007)), which also show that the structure of a number of paclitaxel derivatives were know in the art at the filing date of the present application. Specifically, Miller et al. discloses the structures of a number of paclitaxel derivatives, so called 'second generation taxoids', and also shows the structures of paclitaxel and docetaxel (see Figure 1).

The review by Kingston et al., although published in 2007, cites a number of references disclosing the structures of paclitaxel derivatives which were published prior to filing date of the present application (see for example the second-generation taxoids shown in Figure 2). In addition, this review makes it clear that the structure of paclitaxel serves as the starting skeleton for the generation of new compounds (see abstract), and hence confirms that next-generation taxoids are paclitaxel derivatives.

As for the Examiner's concern for disclosure "indicating the functional characteristics of the "derivatives" when combined with an aurora kinase inhibitor" (see page 10 of the Office Action dated February 14, 2008), the paclitaxel derivative of claim 4 is a taxane. Due to the similarities between their structures, different taxanes also have similar activities with regard to inhibition of mitotic spindle assembly (page 3, lines 2-10). Thus, the functional characteristics of taxanes are coupled to their structure.

Reconsideration and withdrawal of the Section 112, first paragraph "written description", rejection of claim 4 are requested.

The Section 112, first paragraph "enablement", rejection of claims "1-13, 15, 19-21, 26 and 39-41" is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Clarification is requested as to the inclusion of claims "11-13, 15, 19-21, 26 and 39-41" in the rejection as claims 11-32 are indicated as having been withdrawn from consideration (see page 1 of the Office Action dated February 14, 2008) and claims 33-51 were canceled in the Amendment of January 3, 2006.

Claim 1 requires that the recited cancer is a cancer in which Aurora kinase is over-expressed relative to non-cancer cells. Basis for the recitation may be found, for example, on page 11, lines 6 to 7, of the application as filed. Thus, claim 1 relates a defined class of cancers having the specified characteristics.

At the filing date of the present application, Aurora kinase over-expression was known to occur in a number of cancers. For example, it was estimated at the time that Aurora-A over-expression occurred in 12-62% of breast and colorectal cancers (page 1,

lines 31-33). In addition, while paclitaxel and other taxanes were widely used in the treatment of refractory ovarian cancer, breast cancer, and other types of epithelial cancer (page 1, lines 14-17), it was also known that some cancers were resistant to treatment with mitotic-spindle inhibitors (page 1, lines 26-29).

The Examiner states that the example on pages 21-24 of the specification

> "exemplifies that Aurora-A over-expression induces a striking increase in resistance to paclitaxel-induced apoptosis..., which appears to be the opposite of the invention which the Applicant is claiming." See page 15 of the Office Action dated February 14, 2008 (emphasis added).

In fact, the applicants have shown that Aurora-A over-expression dysregulates the spindle checkpoint during carcinogenesis and reduces the sensitivity of cells to mitotic spindle assembly inhibitors such as paclitaxel (page 1, line 31, to page 32, line 3). Specifically, the applicants have demonstrated that over-expression of Aurora-A kinase in HeLa cells, which are normally highly sensitive to paclitaxel, induces resistance to paclitaxel treatment in these cells (page 23, lines 3-13). This data is consistent with the claimed invention, as it demonstrates that the insensitivity to mitotic-spindle inhibitors, such as paclitaxel, observed for many cancers may be due to the over-expression of Aurora kinase in these cancers. It is this insensitivity that the treatment with an Aurora kinase inhibitor in combination with a mitotic spindle assembly inhibitor is intended to address, and this is reflected in claim 1.

The levels of Aurora-A kinase expression observed in HeLa cells correspond to those observed for many cancers (page 23, lines 19-25). In other words, the applicants have demonstrated, for the first time, that there is a nexus between Aurora-A kinase

expression in cancer cells and resistance to paclitaxel. This observation allows one of ordinary skill in the art to make and use methods of the claimed invention wherein inhibition of Aurora-kinase in the recited cancers is likely to improve their responsiveness to treatment with mitotic spindle inhibitors.

This is further supported by the attached paper by Hata et al. ("RNA Interference Targeting Aurora Kinase A Suppresses Tumor Growth and Enhances the Taxane Chemosensitivity in Human Pancreatic Cancer Cells" Cancer Res 2005; 65: (7) April 1, 2005), which discloses that the cytotoxicity of paclitaxel and docetaxel is enhanced by suppression of Aurora A kinase expression in human pancreatic cancer cells (see abstract and page 2902, column 2, paragraph 2 to page 2903, column 1, paragraph 1).

The application also discloses methods for detecting Aurora kinase expression in a given cancer (page 4, line 27 to page 6, line 15; page 15, line 7, to page 17, line 3). Thus, there would be no undue burden on the ordinary skilled person in determining if a given cancer over-expresses Aurora kinase.

The application further discloses exemplary Aurora kinase inhibitors (page 6, lines 17-24) and mitotic spindle inhibitors (page 2, line 20, to page 3, line 33). Methods for administering these compounds to an individual are also disclosed (page 11, line 25, to page 14, line 9), and would in any case be well within the capabilities of the ordinarily skilled medical practitioner, with reasonable experimentation.

Thus, the applicants submit that one of ordinary skill in the art will be able to make and use the claimed invention, without undue experimentation.

Reconsideration and withdrawal of the Section 112, first paragraph "enablement", rejection are requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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